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Anergy in High-Risk Surgical Patients: The Role of Parenteral Nutrition

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The finding of delayed hypersensitivity on skin testing has been used to predict the outcome following operations, traumas or severe illnesses and has been correlated with nutritional status in some reports. To test these hypotheses, we did weekly skin tests with a battery of four antigens on 98 high-risk patients referred to the nutritional support service. Anergy persisted or developed in 72 patients, whereas 26 patients remained or became reactive. These two groups were comparable in number of days in hospital, age and amount and duration of parenteral nutrition. Infectious complications (68 percent versus 23 percent, $P < .001$), sepsis (35 percent versus 12 percent, $P < .01$) and mortality (33 percent versus 0 percent, $P < .001$) were more prevalent in anergic than in reactive patients. There was no correlation between nitrogen balance studies and skin test results. In most instances conversion of skin test results occurred as a consequence of appropriate surgical care rather than nutritional support. Whereas nutritional support is required in these high-risk patients, anergy should not be the sole indicator for giving nutritional support or delaying an operation.

THE PREDICTIVE VALUE of delayed hypersensitivity shown by skin tests has been established for the outcome of surgical procedures, blunt traumas and nonsurgical illnesses.¹⁻⁷ The specific reported association has been between an abnormal skin test response (anergy) and infectious complications, sepsis and mortality. Evidence has also been presented that nutritional support can convert skin test results from anergy to responsiveness and thus improve outcome.⁶⁻¹⁰ Others^{11,12} have failed to confirm these findings. To examine these correlations, we reviewed the records of patients

observed by the Nutritional Support Service (NSS) at Harborview Medical Center (Seattle) over a 12-month period.

Methods and Materials

From May 1979 to May 1980 all patients in Harborview Medical Center who required nutritional support by the parenteral route or by tube feeding or jejunostomy were seen by the NSS. Referring physicians agreed to skin testing in 98 of these patients after nutritional support had been begun. The patients were cared for by a resident team under the direction of an attending physician. They were free to follow NSS suggestions or not, and thus not all patients seen by the NSS were skin tested. The NSS assessed the patients'

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ABBREVIATIONS USED IN TEXT

NSS=Nutritional Support Service
TPN=total parenteral nutrition

nutritional requirements including calories, protein and trace elements, taking into account the degree of trauma, sepsis and weight loss coupled with age and previous diet. A computer program was used to determine recommended support. All of the cases were followed by the NSS until the patient's discharge from hospital.

Patients were tested initially and at weekly intervals with a battery of four skin tests. An intradermal injection of 0.1 ml of each of the following reagents was given: intermediate-strength purified protein derivative, 5 units (PPD, Ormont Drug and Chemical Company, Englewood, New Jersey); streptokinase, 10 units, and streptodornase, 2.5 units (Varidase, Lederle Laboratories, Pearl River, New York); mumps, 2 units (Eli Lilly and Co., Indianapolis, Indiana), and Dermatophitin, (1:100, Hollister-Stear Laboratories, Spokane, Washington). Reaction was recorded after 48 hours and an induration of greater than 5.0 mm in diameter, excluding erythema, was arbitrarily considered positive.¹ If any one test was positive the patient was labeled reactive; if none were positive the patient was considered anergic. Testing and readings were done by a hospital nurse epidemiologist who was experienced in this technique.

Sepsis was defined in patients with a proved infectious focus (with or without positive blood cultures) progressing to an episode of hemodynamic instability requiring support. Infectious complications without sepsis included wound infections, pneumonia, lung abscess or intraabdominal abscess in patients with hemodynamic stability. For purposes of this report, a patient recorded as being in a septic condition was not recorded a second time as having an infectious complication, so that the overall infection rate is the sum of the rate for sepsis and for infection.

Results

A total of 98 patients were included in this study, 34 women and 64 men, with an average age of 56 years (range, 18 to 98 years). In all, 22 patients had elective operations, 38 were victims of blunt or penetrating trauma requiring surgical treatment and 38 were admitted to hospital with acute problems such as myocardial infarc-

TABLE 1.—Reason for Admission to Hospital Correlated With Skin Test Response, Morbidity and Mortality

	Number	Number With Sepsis	Number With Infections	Mortality percent
Elective				
Anergic	13	1	4	3
Reactive	9	0	0	0
Trauma				
Anergic	29	14	11	7
Reactive	9	2	1	0
Urgent				
Anergic	30	12	7	14
Reactive	8	1	2	0

tion, perforated or ischemic bowel, pancreatitis or ruptured abdominal aortic aneurysm. The mean duration of stay in hospital for this nutritionally "high risk" group of patients was 39 days (range, 3 to 140 days). A total of 67 patients received total parenteral nutrition (TPN) for a mean of 19 days (range, 3 to 92 days). The remaining 31 patients received enteral nutrition by small-bore feeding tubes. Each patient received an average of 35 kcal per kg of body weight and 1.2 grams per kg of amino acids per day, with appropriate amounts of fats and trace elements.

Of 98 patients seen, 20 (20 percent) were reactive on skin testing when initially seen by the NSS and remained so throughout follow-up. Six more patients were anergic on initial testing but became reactive during follow-up. A total of 26 (27 percent) were therefore reactive or became reactive during NSS follow-up. Of the total, 70 patients (71 percent) were anergic on initial testing and remained so. Two other patients were initially reactive but became anergic during follow-up. Thus, 73 percent were anergic at the end of the NSS follow-up. Because patients were in some instances still recuperating after the initiation of oral feedings, the skin testing sequence occasionally was longer than one-week intervals.

Of the 26 patients in the *reactive group*, nine (35 percent) were admitted following major trauma, eight (31 percent) were admitted for urgent reasons, such as bowel obstruction or perforated viscus, and nine (35 percent) had an elective operation during their stay in hospital. In the *anergic group*, 29 (40 percent) were admitted following major trauma, 30 (42 percent) had an urgent operation and only 13 (18 percent) had an elective operation (see Table 1). The average ages of the two groups were similar: 52 years for the reactive patients and 58 years for the anergic (P = not significant). In addition, the proportion of

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TABLE 2.—Comparison of Patients Who Were Reactive or Anergic to Skin Testing

	Number	Mean Age	Sex	Hospital Days mean	Receiving TPN percent	Mean Days of TPN
Reactive patients	26	52	20 ♂ 6 ♀	42	62	23
Anergic patients	72	58	44 ♂ 28 ♀	38	71	17

TPN = total parenteral nutrition

elderly patients in each group was similar (27 percent of the reactive patients was over 70 years old, whereas 32 percent of the anergic patients was over 70 years old). The duration of hospital stay was also similar, with reactive patients staying a mean of 42 days and anergic patients staying 38 days ($P = \text{not significant}$). Most of the patients in each group received parenteral nutrition (reactive, 62 percent; anergic, 71 percent) and the remainder of each group received enteral support either by nasogastric, nasoduodenal or jejunostomy feeding tubes. The duration of this parenteral support was approximately three weeks (reactive, 23 days; anergic, 17 days), indicating a relatively high level of nutritional risk in both groups (Table 2).

There were striking differences in mortality and morbidity between these two groups. In the skin-

test reactive group there were no deaths, and there were three patients with sepsis and three with infectious complications, for a combined infectious complication rate of 23 percent. In the anergic group 24 patients died, a mortality of 33 percent. In the anergic group the combined incidence of infectious complications was 49/72 (68 percent), with 27 patients with sepsis and 22 patients with other infectious complications (Table 3). These results are further delineated by reason for admission to hospital in Table 1.

In the anergic group of three patients admitted for elective reasons two died of carcinoma. The remaining 21 patients who died all had unscheduled admissions, and 19 of these died as a result of septic complications. Of 27 patients with sepsis and anergy only seven survived. Thus the mortality in this extremely high-risk group was 74 percent. None of the three reactive patients with an episode of sepsis died ($P < .04$). When the patients are grouped according to the reason for admission (Table 4), there is seen to be a greater incidence of septic complications among the unscheduled patients. Whereas other infectious complications, mortality and anergy were also more common in the unscheduled group, these differences were not statistically significant. There was no significant relationship between skin test reactivity and age (Table 5).

Of the anergic patients, 51 received 35 or more

TABLE 3.—Comparison of Morbidity, Mortality and Skin Test Results

Skin Test Results	Number	Number With Sepsis	Number With Infections	Infectious Complications percent	Mortality percent (number)	Permanent Coma
Reactive	26	3	3	23	0	0
Anergic	72	27	22	68	33 (24)	3
P		.01	.05	<.001	<.001	NS

NS = not significant

TABLE 4.—Morbidity, Mortality and Skin Test Results Versus Indication for Admission to Hospital

Reason for Admission	Number	Reactive number percent	Anergic number percent	Sepsis number percent	Infection number percent	Mortality number percent
Scheduled (elective)	22	9 41	13 59	1 5	4 18	3 14
Unscheduled	76	17 22	59 78	29 38	21 28	21 28
P		NS	NS	.003	NS	NS

NS = not significant

TABLE 5.—Skin Test Results and Age

Skin Test Results	Age								Total
	0-19	20-29	30-39	40-49	50-59	60-69	70-79	80	
Reactive	0	5	2	2	5	5	6	1	26
Anergic	1	9	6	5	12	16	12	11	72

kcal per kg of body weight and 1.2 or more grams of protein per kg per day for an average of 17 days. Thirty-one percent were supported for 25 days or more; none of these patients' skin test responses converted to positive, and one patient's test became anergic after having been initially reactive. This patient had multiple intraabdominal abscesses and received parenteral nutritional support for 84 days. Another patient became anergic while receiving adequate enteral nutrition but with a very complicated postoperative course. Only six patients converted to reactivity after having initially been anergic. Five of these six received TPN for an average of 42 days. Two patients converted to reactivity following resection of ischemic bowel. Two patients became reactive after recovering from operations for trauma.

Weekly nitrogen balance (NB) studies using 24-hour urine urea nitrogen determinations⁷ were carried out on nine patients while they were receiving parenteral nutrition ($\text{NB} = \text{nitrogen in} - [\text{urine nitrogen determination} + 4]$). Nitrogen losses in fistula or drains were also measured when appropriate and added to the minus side of the equation. Seven of the nine were in positive balance. Five of these seven remained anergic. The remaining two patients converted to skin-test reactivity after attaining positive nitrogen balance in conjunction with appropriate surgical care. The two patients who were in negative nitrogen balance both remained anergic.

Discussion

Palmer and Reed¹³ have reported that 91 percent of patients in hospital who are not severely ill will respond to at least one of the four standard skin tests. This was confirmed by Grossman and co-workers,¹⁴ who also noted no significant differences in response with increasing age. Meakins and associates¹ have acquired extensive experience in the use of skin testing to predict outcome of patients in hospital. Their results in 1,332 patients indicated a 36 percent mortality and a 52 percent infectious complication rate in anergic patients, whereas reactive patients had a 4 percent mortality and a 10 percent infectious complication rate. These results were consistent for preoperative, postoperative and trauma cases.¹⁰ In addition, sequential testing showed a 2.1 percent mortality in patients who were initially reactive or whose skin test results showed improvement. In this same group of patients there was a 21 percent infectious complication rate. But those who were

initially anergic or who worsened had a 74 percent mortality and a 65 percent infectious complication rate.¹⁵ Pietsch and colleagues¹⁰ showed an association of anergy with sepsis, hemorrhage and age combined with degree of trauma. Anergy was not associated with uncomplicated cancer, nor with age alone.¹⁰ In 50 consecutive elective cases of cholecystectomies reported on by Pietsch and co-workers,^{10,16} there were no anergic patients, suggesting that operation alone does not affect skin test results. Others²⁻⁷ have reported a similar predictive value for skin tests. Brown and associates¹² and Ryan and Taft¹¹ independently found no predictive value for skin testing in solely elective preoperative cases.

Thus, data suggest that response to four standard skin tests can predict outcome following operation or injury and that conversion of anergy to skin test reactivity predicts an improved outcome.⁶⁻¹⁰ Whereas several reports⁶⁻¹⁰ have attempted to correlate skin test response to nutritional status, Meakins and colleagues¹ have shown that selected anergic patients can convert to reactivity by appropriate surgical care nearly 84 percent of the time.

It was our impression that factors other than nutritional support were important in affecting skin test responsiveness in our patient population. A review of our experience was thus organized to examine this question. It has been previously shown^{10,16} that outcome following minor degrees of trauma or surgical procedure was not predicted by skin test results. For this reason we included only those high-risk patients who were judged by their primary clinicians to require intensive nutritional support. There was no statistically significant difference between the reactive and anergic groups in the age, sex, duration of hospital stay, percentage of the groups receiving parenteral nutrition or duration of parenteral nutrition. Thus, these factors did not appear to influence outcome between the two groups. The proportion of elective and nonelective cases in each group was also similar.

Most (73 percent) of the patients in our study were anergic. This is in contrast to other reports in which most patients were reactive.^{1-3,5-7} This may be due to the high-risk nature of a group of patients selected solely on the basis of their need for nutritional support.

Our data confirm previous reports that anergic patients have a statistically significant increase in

morbidity and mortality when compared with reactive patients. Anergic patients with sepsis had a 74 percent mortality. Reactive patients rarely became septic (12 percent), whereas anergic patients had a 38 percent incidence of sepsis. While sepsis developed in 31 percent of all of these patients, 90 percent of them were in the anergic group. Thus, there appears to be a strong association between anergy and sepsis in this group of patients. Ryan and Taft¹¹ and Brown and co-workers,¹² however, did not confirm such a relationship in a group of low-risk patients, all of whom were admitted for an elective operation.

Our data suggest that nutritional support alone will not convert skin test response or improve outcome. Only two of six patients who converted to reactivity appeared to do so primarily because of parenteral nutrition. This was in spite of aggressive nutritional support averaging 42 days in duration with 35 kcal per kg of body weight and 1.2 grams of protein per kg. Most patients who converted to reactivity did so following appropriate medical and surgical care in addition to nutritional support (four of six). Of the anergic patients, 51 received adequate parenteral nutrition for an average of 17 days, with no difference in skin test responsiveness; this included 11 who received 25 days or more and 4 who received more than 40 days of parenteral nutrition. Previous reports^{7-9,17} have established that the average time required to convert skin tests in animals and humans is near 18 days. Although our patients received appropriate nutritional support for this length of time, skin test reactivity did not improve in most of the anergic patients. This does not mean that nutritional support was not helpful, but that it was used as a supportive and not a treatment measure.

We were unable to show a correlation of positive nitrogen balance with skin test conversion in a small group of patients. Haffee and Angorn¹⁸ also failed to show this relationship in patients with esophageal carcinoma.

Thus, based on our experience and that of others, we think that skin test responsiveness does correlate with eventual outcome but that in most cases this outcome is most strongly affected by conventional medical and surgical treatment. Skin testing is a complex procedure that measures a host's ability to put together a number of physiologic processes. It is affected by, but not a direct measure of, nutrition, trauma, sepsis, tumor burden and medication effect. An anergic patient is at high risk for the development of life-threatening

complications and must be treated appropriately and expeditiously. Skin test results can be used as one marker for identifying high-risk patients but do not provide a reliable index for designing specific therapy or corrective measures and do not justify altering otherwise standard treatment regimens. Our data are consistent with the hypothesis of Mullen and associates¹⁹ that only in very high-risk patients, as defined by the Prognostic Nutritional Index,^{20,21} does parenteral nutrition seem to effect a decrease in incidence of postoperative complications. Parenteral nutrition is required in nutritionally depleted patients as a supportive adjunct regardless of skin test results. In the absence of other indicators of malnutrition, anergy should not be the sole indication for parenteral nutrition or for delay of surgical intervention.

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